Practice-Based Evidence Study Design for Comparative Effectiveness Research

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Objectives: To describe a new, rigorous, comprehensive practice-based evidence for clinical practice improvement (PBE-CPI) study methodology, and compare its features, advantages, and disadvantages to those of randomized controlled trials and sophisticated statistical methods for comparative effectiveness research.

Research Design: PBE-CPI incorporates natural variation within data from routine clinical practice to determine what works, for whom, when, and at what cost. It uses the knowledge of front-line caregivers, who develop study questions and define variables as part of a transdisciplinary team. Its comprehensive measurement framework provides a basis for analyses of significant bivariate and multivariate associations between treatments and outcomes, controlling for patient differences, such as severity of illness.

Results: PBE-CPI studies can uncover better practices more quickly than randomized controlled trials or sophisticated statistical methods, while achieving many of the same advantages. We present examples of actionable findings from PBE-CPI studies in postacute care settings related to comparative effectiveness of medications, nutritional support approaches, incontinence products, physical therapy activities, and other services.

Conclusions: Outcomes improved when practices associated with better outcomes in PBE-CPI analyses were adopted in practice.

Key Words: practice-based evidence, clinical practice variations, comparative treatment outcomes

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Many researchers have written about problems with evidence from evidence-based medicine (EBM), whose main tools are randomized trials and meta-analysis.[1–3] Westfall states "What is efficacious in randomized clinical trials is not always effective in the real world of day-to-day practice . . .. Practice-based research provides the laboratory that will help generate new knowledge and bridge the chasm between recommended care and improved care." Although randomized controlled trials (RCTs) are important to confirm whether a new treatment causes an effect, they are unlikely to discover combinations of interventions or practices that are effective and efficient in routine care.

Porter and Teisberg[3] call for determining the best treatments for specific types of patients. They feel that encouraging competition at the level of treatments for specific diseases or co-occurring conditions and types of patients will speed the development of the right kind of information and improve value (quality of health outcomes per dollar expended).

To rise to Porter and Teisberg's challenge, we must develop scientifically rigorous methods that answer questions such as, "Does the treatment work in the real world of everyday practice?" or "For whom does the intervention work best?" These questions differ from typical RCT questions: "Does the investigational treatment cause an effect?" or "How and why does the intervention work?" Trials that address the latter questions are designed to maximize the chance that some effect of a new or existing treatment will be revealed by the study, and to provide a confirmatory analysis of the original study hypothesis.

In this article, we describe a practice-based evidence for clinical practice improvement (PBE-CPI) research methodology that fills gaps in information needed by clinical and health policy decision makers.[1,4] As a clinical research method, PBE-CPI embraces all 4 elements of practical clinical trials (PCTs) for which the hypothesis and study design are developed specifically to answer the questions faced by decision makers. Characteristic features of PCTs are: (1) select clinically relevant alternative interventions to compare, (2) include a diverse population of study participants, (3) recruit participants from heterogeneous practice settings, and (4) collect data on a broad range of health outcomes.[1] The PBE-CPI method provides a way to operationalize PCTs effectively.[5] We compare RCTs, sophisticated statistical tests, and PBE-CPI research methodologies for comparative effectiveness by evaluating their relative strengths and weaknesses and present several examples of comparative effectiveness findings from PBE-CPI studies.

METHODS

Randomized Controlled Trials: Features and Challenges

RCTs are considered the gold standard for establishing causality in scientific research. The intellectual origins of RCTs lie in agriculture: in agricultural hothouses, the environment can be reasonably controlled and various interventions can be tested. Likewise, in RCTs in health services research, study participants are randomized into either a treatment or a control arm, so that participant differences can be eliminated and the effect of the treatment can be isolated. With nonrandomized comparison groups, some nontreatment effects may remain unaccounted for and the outcomes may not result from the treatment or intervention under study.

RCTs use relatively simple computations and fairly small sample sizes, which were well suited to the computational limitations of an earlier time. RCTs do not need or use the full power of multivariate statistics in which many variables can be considered simultaneously and covariates can be identified and neutralized to evaluate intervention effects. Instead they use randomization in an attempt to neutralize unmeasured confounders; measured confounders are used to exclude patients from study.

In the research world, anything less than RCT-level evidence has been considered suspect by many. However, RCTs in health services research present several major challenges. Here, we describe some of these challenges and subsequently discuss how a PBE-CPI approach is liberated from many of them.

Standardization and Artificiality

RCTs use standardized treatment protocols and hold variables constant to isolate effects of the intervention and reduce "noise" in data. Hence, the intervention setting may not reflect the real-world clinical environment. Standardized treatment protocols require extensive quality control to decrease errors in treatment delivery, but treatment purity is difficult to maintain over time, across centers, and across clinicians. If this purity is compromised, intention-to-treat analyses (which keep all participants in the study and in their assigned groups even if the treatment protocol or control is not followed as prescribed) may be the best analysis option. Unfortunately, results of ITT analyses do not reflect efficacy of the treatment being studied, because some patients in the treatment group do not receive the treatment.

Selection Criteria, Patient Recruitment, and Generalizability

To reduce variation among study participants, selection criteria are often restrictive, which limits generalizability of study findings (external validity). For example, many studies exclude subjects with comorbidities, although significant comorbidities are common in many populations and may alter outcomes. Also, due to restrictive selection criteria, clinicians sometimes dismiss RCT findings, because they believe their patients are materially different from those in a clinical trial. Restrictive selection criteria typically mean that only a small percentage of patients—usually 10% to 15%—are eligible for a trial. Often, enormous resources are expended to locate individuals who meet selection criteria and achieve desired sample sizes.

Blinding

RCTs use some degree of blinding. Ideally, the study participant, clinician, and researcher or observer should be unaware of whether the participant is in the treatment or control arm. As a practical compromise, double-blinding, defined as blinding of the participant and either the clinician or the researcher/observer, is often used. However, many interventions do not lend themselves well to blinding of any kind (eg, many physical therapy interventions, or use of certain equipment).

Cost

Elaborate protocols to screen patients, coordinate and monitor care, and collect data make RCTs expensive. For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) followed 1493 patients and cost $64 million.

Summary

Because of their design characteristics, findings from RCTs do not always reflect comparative effectiveness of treatments for all types of patients in routine practice. Alternative study designs should be considered.

Observational Data and Causal Inferences

Confidence in a treatment depends on confidence in the evidence supporting a causal connection between the treatment and a patients' improved condition. Although randomization encourages this confidence, RCT evidence can be costly to obtain, may not be broadly applicable in a real-world clinical context, and can easily be compromised by small protocol deviations. An alternative is to use data that measure characteristics of patients and their treatments. However, if these data are not obtained using participant randomization, it can be difficult to determine whether different outcomes should be attributed to different treatments or to patient differences.

To overcome these problems, methods have been developed to compute unbiased estimates of treatment effects using observational data and controlling for unmeasured confounders.[6–12] Drawbacks to these methods, however, include their sensitivity to untestable assumptions and the need for sophisticated statistical knowledge to ensure appropriate adjustment for relevant factors. These drawbacks make findings less understandable to clinical decision makers. As an alternative, the method of instrumental variables was developed to estimate treatment effects using observational data when unobserved confounders are present.[13] However, the treatment effect is instrument-specific, and the assumptions are again untestable.

A pragmatic way to reduce uncertainty about comparative effectiveness of treatments is to collect comprehensive patient, treatment, and outcome data that are suggested by transdisciplinary clinicians who treat the types of patients being studied. One such approach, PBE-CPI, aims to foster confidence in the generalizability of its findings, and step

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over the technical concerns about assumptions that are inherent in the use of instrumental variables or unbiased estimation. PBE-CPI accepts uncertainty regarding potential alternative explanations while minimizing the likelihood of such explanations.

Practice-Based Evidence for Clinical Practice Improvement: Features and Challenges

Comparative features of RCTs and PBE-CPI study methodologies are listed in Table 1. PBE-CPI harnesses the complexity of patient and treatment differences in the actual practice of care.[5] Unlike an RCT, it does not alter the treatment to evaluate efficacy of a particular intervention. Instead, it captures in-depth, comprehensive information about patient characteristics, processes of care, and outcomes to characterize the process of care and ascertain the contribution of individual processes to outcomes, controlling for patient differences. PBE-CPI is a type of observational study design with 7 significant features:

1. all interventions are considered to determine the relative contribution of each,
2. hypotheses are general,
3. minimal patient selection criteria maximize generalizability and external validity,
4. detailed characterization of patients through use of robust measures of severity of illness and functional status,
5. patient differences are controlled statistically rather than through randomization,
6. facility and clinical buy-in obtained through use of transdisciplinary Clinical Practice Team, and
7. high level of transparency for all stakeholders.

Steps used to conduct PBE-CPI studies are:

1. Establish a multisite, transdisciplinary Clinical Practice Team composed of Center medical director or lead researcher and clinicians of various disciplines to engage in an iterative process to (*a*) define key patient characteristics presumed to affect outcomes and/or effectiveness of therapies, (*b*) identify and define individual components of each discipline's care process, (*c*) create discipline-specific documentation tools to quantify the delivery of those components, and (*d*) incorporate documentation into routine facility practices. Study clinicians select factors that may influence outcomes based on theoretical understand-

TABLE 1. Comparison of Randomized Controlled Trials and Practice-Based Evidence for Clinical Practice Improvement Studies

Variables	Randomized Controlled Trials	Clinical Practice Improvement
Patient variables	Patient eligibility and stratification factors	Patient eligibility and stratification factors
	Eliminate patients who could bias results: comorbidities, more serious disease, etc.	Use severity of illness to measure comorbidities and disease severity
	About 10–15% of patients qualify	All patients qualify by measuring patient differences; none excluded
Process variables	Treatment protocol	Measure or record all treatments and interventions
	Specify explicitly every important element of the process of care for both treatment and control arms	Abstract information from charts based on existing practice
	Informed consent	Informed consent often not needed*
Outcome variables	Powered for primary outcome	Many outcomes assessed
	Change based on evidence	Improvement based on evidence from analyses of data
Measurements/documentation	Limited number of patient variables, treatments, outcomes measured	Comprehensive holistic framework
	Variables specified precisely for all patient, treatment, and outcome measures	Variables specified precisely for all patient, treatment, and outcome measures
Database	Limited to the variables needed	Comprehensive and detailed
Result	Efficacy	Effectiveness
	Assigned causality	Association and assumed causality
Hypotheses	Typically 1 hypothesis	Typically many hypotheses
	Clearly defined at the start	Many and broad at the start
	Narrow and focused	Refined and new hypotheses generated by analytic findings
Local knowledge	Not dependent on local knowledge	Depends on local knowledge; entails participation by practicing clinicians
Confounders	Assumed not relevant to study or outcome—eliminated in study design	Do affect outcomes and are relevant to include

*Informed consent may not be required if there is no experimental intervention and if no data are collected beyond what is ascertained from medical records and from reports prepared by clinicians in the course of usual care.

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ing, published research evidence and guidelines, and clinical experience.
2. Use the Comprehensive Severity Index (CSI) to control for differences in patient severity of illness, including comorbidities that might otherwise affect outcomes. CSI is an age- and disease-specific measure of physiologic and psychosocial complexity comprised of over 2200 signs, symptoms, and physical findings.
3. Implement an intensive data collection protocol that captures data on patient characteristics, care processes, and outcomes drawn from medical records and study-specific point-of-care data collection instruments. Use multiple quality assurance methods, including training, internal reliability testing, and external review.
4. Create a study database suitable for statistical analyses.
5. Successively test a priori and post hoc hypotheses based on questions that motivated the study originally, previous studies, existing guidelines, and, above all, hypotheses proposed by the Clinical Practice Team using bivariate and multivariable analyses, including multiple regression, analysis of variance, logistic regression, hierarchical models, and other methods consistent with measurement properties of key variables.
6. Implement and evaluate findings from step 5 to determine whether the new or modified interventions replicate results identified in earlier phases.
7. Incorporate validated study findings into standard practice of care and care protocols.

In summary, PBE-CPI studies encompass all care management processes and include: (1) key patient characteristics (including disease-specific physiologic severity of illness and psychosocial abnormalities presented at each visit or each admission); (2) all treatment and care processes (including medications, nutritional treatments, surgical and nonsurgical interventions, and therapies); and (3) multiple outcome measurements.

Patient Factors and the CSI

Patient factors are key characteristics of the study population, such as demographic characteristics, indications for treatment (eg, ruptured appendix), severity of illness, initial functional status, and psychosocial factors. By incorporating detailed information about patients and accounting for differences through statistical analyses, a PBE-CPI design achieves some of the benefit that RCTs accomplish through randomization of patients after excluding patients with factors that could bias the findings. Detailed patient profile data include condition-specific physiologic data such as those in the CSI.[5,14–20] The CSI is used in data analysis as a covariate to balance the impact of the principal diagnosis along with comorbid and co-occurring conditions. This use of CSI helps detect differences that might otherwise be hidden or washed out by the effect of overall severity. CSI is a software application that produces disease-specific physiologic severity of illness scores that can be used to control for severity differences at the individual criterion level. Previous research has shown that CSI is a reliable and valid measure of illness severity in multiple clinical populations. Over 20 large, multicenter PBE-CPI studies using CSI have been conducted.

Care Process Factors and Capturing Details About Treatments at Point-of-Care

A process of care is a sequence of linked, usually sequential, steps designed to cause desired outcomes. The goal is to find measurable factors that describe each process step. Examples include which drugs are dispensed, which dose is used, which nutritional therapies are used and for how long, or which physical therapy activities/interventions are used and for how long. A data collection instrument records the process steps in detail, including timing and dates. Frontline clinicians characterize their interventions fully and accurately. Thus, PBE-CPI studies provide a very detailed account of processes and interventions. An example of a point-of-care documentation form used by physical therapists in stroke rehabilitation is presented in Figure 1. It took between 0.5 and 2 minutes to fill this out for each physical therapy session.

Outcome Factors

Commonly assessed outcomes include condition-specific complications, condition-specific long-term medical outcomes (based on clinician assessment or patient self-report), patient functional status, patient satisfaction, and cost. Outcome factors are PBE-CPI analogs of assessment endpoints in an RCT.

Analyses

Detailed data are captured in PBE-CPI studies to create a large study database that includes all the patient, process, and outcome variables of interest. Multivariable statistical methods are then used to compare alternative treatments while controlling for other variables that may drive observed differences between treatments and outcomes. These statistical methods allow researchers and clinicians to examine relationships that are more complex than those that they could examine if they were to use one explanatory or treatment variable at a time (or even a few). The significant independent variables in regression equations identify key process steps that are associated with better or worse outcomes when patient factors are controlled for. CPI methodology allows important statistical associations to be identified. Controversial or unexpected findings can be challenged and corroborated or disproved by examining various data subsets with different patient and treatment characteristics. Although causality cannot be assigned, alternate hypotheses regarding possible cause and effect can be tested using the large number of available variables to identify mediating and moderating influences on outcomes. Results of these analyses can be used to eliminate potential hypotheses regarding causality, and to generate specific analytic questions. There is no minimal effect size in PBE-CPI studies; effect sizes change as we examine finer and finer subgroups of patients.

PBE-CPI focuses on actionable findings that can be implemented to improve effectiveness of care. This focus

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Physical Therapy Rehabilitation Activities

Patient ID: Sample

Date of Therapy Session: / /

Therapist:

Time session begins: :

INTERVENTION CODES

Neuromuscular Interventions:
01. Balance training
02. Postural awareness
03. Motor learning
04. PNF
05. NDT
06. Gait with body weight support
07. Involved upper extremity addressed
08. Constrained induced movement therapy

Musculoskeletal Interventions:
09. Strengthening
10. Mobilization
11. PROM/Stretching
12. Manual Therapy
13. Motor Control

Cardiopulmonary Intervention:
14. Breathing
15. Aerobic/Conditioning exercises

Cognitive/Perceptual/Sensory Interventions:
16. Cognitive training
17. Perceptual training
18. Visual training
19. Sensory training

Education Interventions:
20. Patient
21. Family/Caregiver
22. Staff

Equipment Interventions:
23. Prescription/Selection
24. Application
25. Fabrication
26. Ordering

Modality Interventions:
27. Electrical Stimulation
28. Biofeedback
29. Ultrasound

Pet Therapy:
30. Use of dog
31. Use of other animal

Assistive Device:
32. Ankle dorsi flex assist
33. Cane - Large base
34. Cane - Small base
35. Cane - Straight
36. Crutches - Axillary
37. Crutches - Forearm
38. Crutches - Small base forearm
39. Dowel
40. Grocery cart
41. Hemirail
42. Ironing board
43. KAFO
44. Lite gait
45. Mirror
46. Parallel bars
47. Platform (parallel bars or FWW)
48. Standing frame
49. Steps (various heights)
50. Step ladder
51. Swedish knee cage
52. Swiss ball
53. Tray table
54. Walker - FWW
55. Walker - Hemiwalker
56. Walker - Rising Star
57. Walker - Standard
58. Wheelchair

Other:
59.

Area Involved/non-functional:
60. Upper Extremity
61. Lower Extremity
62. Trunk
63. Head/Neck

	Duration of Activity: Enter in 5 minute increments.	Interventions: Enter one intervention code per group of boxes.				
Pre-Functional Activity						
Bed Mobility						
Sitting						
Transfers						
Sit-to-Stand						
Wheelchair Mobility						
Pre-gait						
Gait						
Advanced Gait						
Community Mobility						
Intervention not related to functional activity						
Intervention #2 not related to functional activity						

Co-Treat:
No. of minutes: Disciplines:

Patient Assessment:
Formal Assessment (initial, re-evaluation, discharge): minutes
Home Evaluation: minutes
Work Site Evaluation: minutes

Physical Therapy Time:

Physical Therapist	PT Assistant	PT Aide/Tech	PT Student
minutes	minutes	minutes	minutes

Group Physical Therapy Time:
PT Group/Dovetail: minutes
Enter the number of each that participated in the Group PT:

Patients	Therapists	Assistants	Aides/Techs	Students

FIGURE 1. A point-of-care documentation form used by physical therapists in stroke rehabilitation.

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means that clinicians from all disciplines treating the study patients are involved in study design, defining study variables, study execution, data analysis, and implementation of study findings. Provider involvement at all phases of the study also facilitates buy-in from others that is needed to implement findings and improve care processes.

RESULTS

More than 20 major PBE-CPI studies have been conducted. They have demonstrated that PBE-CPI studies can reveal important comparative effectiveness associations in many diagnostic groups (eg, hip replacement) or disease states (eg, osteoarthritis) and in various clinical settings.[21–33] Comparative effectiveness findings from 2 studies in postacute care illustrate this.

Practice-Based Evidence for Clinical Practice Improvement in Long-term Care

The National Pressure Ulcer Long-Term Care Study (NPULS) was a PBE-CPI study to identify resident, treatment, and facility characteristics associated with pressure ulcer development in nursing home residents.[26] NPULS differs from previous studies in the details collected about residents, treatments, and outcomes. Retrospective data were abstracted from medical records of 1524 residents (from 95 long-term care facilities) who were at risk for developing pressure ulcers. No resident started with a pressure ulcer, but 29% of residents developed one by the end of the 12-week study. Interventions identified by regression analyses to be associated with decreased likelihood of pressure ulcer development included nutritional interventions (use of oral medical nutritional supplements or tube feeding for more than 21 days), use of a combination of new selective serotonin-reuptake inhibitor (SSRI) and new antipsychotic medications, use of disposable briefs for more than 14 days, and 30–40 minutes of registered nurse direct care time per resident per day. Before the study, the nursing homes used many different treatments and products to deal with decreased nutritional intake, weight loss, incontinence, and behavior problems. After better interventions were determined by the NPULS and were implemented consistently, development of new pressure ulcers decreased up to 65%.

Practice-Based Evidence for Clinical Practice Improvement in Stroke Rehabilitation

The Post-Stroke Rehabilitation Outcomes Project (PSROP) was a PBE-CPI study that evaluated associations among stroke rehabilitation patients, processes, and outcomes.[33] Medical directors of 6 study stroke units along with physical, occupational, recreational, and speech-language therapists, psychologists, social workers, and nurses from each site collaborated to create point-of-care documentation forms to record details about each interaction and therapy session with their stroke patients. Subsequently, the clinical teams helped with data analyses.

The activities and interventions associated with better outcomes (controlling for patient differences) included: earlier start of rehabilitation after stroke onset; more time spent per day in higher level rehabilitation activities such as gait, upper extremity control, and problem solving; use of newer psychiatric medications; and enteral feeding. Several findings contradicted conventional practice, such as starting rehabilitation with higher level, more complex activities, even for the lowest functioning patients. Also, use of newer SSRIs (citalopram, escitalopram), opioid analgesics (codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, propoxyphene), and atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone) was associated with greater increases in functional levels from admission to discharge. Enteral tube feeding was significantly associated with greater increases in cognitive and motor functioning for severe stroke patients, even when the degree of dysphagia was controlled for.

PSROP regression analyses produced 2 surprising consistent findings. The first was that "earlier is better." The more quickly a patient started inpatient rehabilitation after a stroke, the better the outcomes were, no matter how sick the patient was at admission (ie, no matter how low the admission functioning score was or how high the CSI score was).

The second finding supported more aggressive therapy at the onset. For example, earlier gait activities, particularly in the first 3 hours of physical therapy, were significantly associated with better outcomes, regardless of how much additional therapy a patient received. Also, participation in higher-order or more difficult therapeutic activities seemed to improve lower-level functional activities, even when the patient did not focus direct attention on those activities. For example, gait training during the first 3 hours of therapy was strongly associated with greater independence in toilet transfers by the time of discharge, after controlling for baseline functioning.

DISCUSSION

In everyday practice, patients are assigned to different treatments based on the provider's medical judgment, compliance is not artificially influenced, and monitoring of results is based on the provider's need for information about a patient's condition. Multiple interventions from multiple professionals are provided concurrently. Interaction of interventions may significantly influence outcomes. The relatively small, nonsignificant effects of a single intervention may be magnified when used in combination with other interventions. Interventions that seem effective in isolation may be antagonistic when provided together. In addition, effectiveness of combinations of interventions is likely to be different for different patients. It is impossible for a randomized clinical trial to test all possible interactions among interventions encountered in routine practice. However, the large natural variation encountered in current practice within and between facilities affords an opportunity to examine the relative effectiveness of combinations and intensities of interventions. PBE-CPI methodology provides a naturalistic view of medical treatments based on data easily documented by medical providers. This view is critical to determine comparative effectiveness of treatment alternatives. PBE-CPI analyses can be used to evaluate current practices and de-

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velop evidence-based improvements based on clinical data rather than clinical opinion.

The PBE-CPI approach contrasts with the approach of traditional RCTs. Because their participants are screened, selected, and subjected to scrutiny and intervention control beyond that occurring in everyday treatment, RCTs sometimes report results that are not broadly applicable in everyday treatment.[34] PBE-CPI methodology identifies medications and interventions that are associated with better outcomes for specific types of patients in real-world practice.

Another key advantage of PBE-CPI study methods is cost. Using existing data from medical records and point-of-care documentation is generally less expensive than implementing a prospective RCT. For example, PBE-CPI studies to date have had sample sizes ranging from 1000 to 2500 patients and have cost between $1 and $5 million. RCTs with similar sample sizes can cost more than 20 times as much and answer only a few questions.

In past PBE-CPI studies, patient consent has been unnecessary because the studies do not involve any change in treatment and are considered quality improvement studies. PBE-CPI studies have received expedited review from IRBs.

Observational studies do not prove causality of underlying relationships, but they can identify hypotheses that can be evaluated clinically. There are 3 approaches to causality determination from PBE-CPI studies: (1) no confounders cause a significant association to disappear; (2) a change in outcome follows a change in treatment as predicted by the PBE-CPI analyses[5]; and (3) repeated studies on the same topic yield the same findings. PBE-CPI studies have demonstrated predictive validity: outcomes improve when practices associated with better outcomes in the PBE-CPI analyses are adopted.

Possible limitations for the PBE-CPI methodology include:

1. Data sources. PBE-CPI studies require detailed data not present in administrative claims databases. PBE-CPI studies work with front-line clinicians to determine variables to collect that either are present in existing medical charts or can be obtained using point-of-care documentation forms.
2. Missing important confounders. PBE-CPI studies attempt to identify confounders by working with front-line clinicians who define relevant patient, treatment, and outcome variables.
3. Incomplete documentation. PBE-CPI studies use site study coordinators who monitor daily documentation for data completeness.

Methodologic alternatives such as PBE-CPI do not replace RCTs; rather, they provide additional systematic outcomes information to improve clinical practice. RCTs and PBE-CPI should be considered complementary study methodologies. Effectiveness of treatments from RCTs can be tested in PBE-CPI studies and PBE-CPI can be a progenitor of new RCTs.

PBE-CPI studies enable healthcare providers, managed care organizations, payers, and individuals to compare the effectiveness of treatments in current practice and improve clinical decision making. They answer questions in the real world, where multiple variables and factors can affect outcomes.

REFERENCES

1. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003;290:1624–1632.
2. Westfall JM, Mold J, Fagnan L. Practice-based research—"Blue Highways" on the NIH Roadmap. *JAMA*. 2007;297:403–406.
3. Porter ME, Teisberg EO. Redefining competition in health care. *Harv Bus Rev*. 2004;82:64–76, 136.
4. Berwick DM. The John Eisenberg Lecture: health services research as a citizen in improvement. *Health Serv Res*. 2005;40:317–336.
5. Horn SD, ed. *Clinical Practice Improvement Methodology: Implementation and Evaluation*. New York, NY: Faulkner & Gray; 1997.
6. Pearl J. Causal inference in the health sciences: a conceptual introduction. *Health Serv Outcomes Res Methodol*. 2002;2:189–220.
7. Pearl J. Statistics and causal inference: a review. *Test*. 2003;12:281–345.
8. Rosenbaum PR. *Observational Studies*. New York, NY: Springer; 2002.
9. Heckman JJ. Micro data, heterogeneity, and the evaluation of public policy: Nobel lecture. *J Polit Econ*. 2001;109:673–748.
10. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Annu Rev Public Health*. 2000;21:121–145.
11. Winship C, Morgan SL. The estimation of causal effects from observational data. *Annu Rev Sociol*. 1999;25:659–706.
12. Winship C, Mare RD. Models for sample selection bias. *Annu Rev Sociol*. 1992;18:327–350.
13. Newhouse JP, McClellan M. Econometrics in outcomes research: the use of instrumental variables. *Annu Rev Public Health*. 1998;19:17–34.
14. Averill RF, McGuire TE, Manning BE, et al. A study of the relationship between severity of illness and hospital cost in New Jersey hospitals. *Health Serv Res*. 1992;27:587–612.
15. Clemmer TP, Spuhler VJ, Oniki TA, et al. Results of a collaborative quality improvement program on outcomes and costs in a tertiary critical care unit. *Crit Care Med*. 1999;27:1768–1774.
16. Horn SD, Torres A Jr, Willson D, et al. Development of a pediatric age- and disease-specific severity measure. *J Pediatr*. 2002;141:496–503.
17. Willson DF, Horn SD, Smout R, et al. Severity assessment in children hospitalized with bronchiolitis using the pediatric component of the Comprehensive Severity Index. *Pediatr Crit Care Med*. 2000;1:127–132.
18. Ryser DK, Egger MJ, Horn SD, et al. Measuring medical complexity during inpatient rehabilitation after traumatic brain injury. *Arch Phys Med Rehabil*. 2005;86:1108–1117.
19. Horn SD, Sharkey PD, Buckle JM, et al. The relationship between severity of illness and hospital length of stay and mortality. *Med Care*. 1991;29:305–317.
20. Gassaway JV, Horn SD, DeJong G, et al. Applying the clinical practice improvement approach to stroke rehabilitation: methods used and baseline results. *Arch Phys Med Rehabil*. 2005;86(12 Suppl 2):S16–S33.
21. Bartels SJ, Horn S, Sharkey P, et al. Treatment of depression in older primary care patients in health maintenance organizations. *Int J Psychiatry Med*. 1997;27:215–231.
22. Bartels SJ, Horn SD, Smout RJ, et al. Agitation and depression in frail nursing home elderly with dementia: treatment characteristics and service use. *Am J Geriatr Psychiatry*. 2003;11:231–238.
23. Horn SD, Sharkey PD, Tracy DM, et al. Intended and unintended consequences of HMO cost containment strategies: results from the Managed Care Outcomes Project. *Am J Manag Care*. 1996;2:253–264.
24. Horn SD, Wright HL, Couperus JJ, et al. Association between patient-controlled analgesia pump use and post-operative surgical site infection in intestinal surgery patients. *Surg Infect (Larchmt)*. 2002;3:109–118.
25. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. *J Pediatr*. 2003;143(5 Suppl):S133–S141.
26. Horn SD, Bender SA, Ferguson ML, et al. The National Pressure Ulcer Long-Term Care Study: pressure ulcer development in long-term care residents. *J Am Geriatr Soc*. 2004;52:359–567.
27. Neumayer LA, Smout RJ, Horn HG, et al. Early and sufficient feeding

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reduces length of stay and charges in surgical patients. *J Surg Res*. 2001;95:73–77.
28. Willson DF, Horn SD, Hendley JO, et al. The effect of practice variation on resource utilization in infants hospitalized for viral lower respiratory illness. *Pediatrics*. 2001;108:851–855.
29. Willson DF, Landrigan CP, Horn SD, et al. Complications in infants hospitalized for bronchiolitis or respiratory syncytial virus pneumonia. *J Pediatr*. 2003;143(5 Suppl):S142–S149.
30. Horn SD, Sharkey PD, Phillips-Harris C. Formulary limitations in the elderly: results from the Managed Care Outcomes Project. *Am J Manag Care*. 1998;4:1105–1113.
31. Horn SD, Sharkey PD, Kelly HW, et al. Newness of drugs and use of HMO services by asthma patients. *Ann Pharmacother*. 2001;35:990–996.
32. Blonde L, Ginsberg GH, Horn S, et al. Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2002;25:245–246.
33. Horn SD, DeJong G, Smout R, et al. Stroke rehabilitation patients, practice, and outcomes: is earlier and more aggressive therapy better? *Arch Phys Med Rehabil*. 2005;86(12 Suppl 2):S101–S114.
34. McMurray JJ, O'Meara E. Treatment of heart failure with spironolactone-trial and tribulations. *N Engl J Med*. 2004;351:526–528.

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